U.S. FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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ALLERGENIC PRODUCTS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY
MARCH 18, 2009

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The meeting convened at 8:00 a.m. in the Conference Room at 5630 Fishers Lane, Rockville, Maryland, Fred Atkins, Chair, presiding.

COMMITTEE MEMBERS PRESENT:

FRED M. ATKINS, M.D., Chair
LINDA S. COX, M.D., Member
SANDRA J. FUSCO-WALKER, Consumer Representative
J. ANDREW GRANT, M.D., Member
ROBERT G. HAMILTON, M.D., Member

GREG A. PLUNKETT, Ph.D., Industry Representative
GILLIAN M. SHEPHERD, M.D., Member

CONSULTANTS:

BRYAN L. MARTIN, D.O., Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University
MICHAEL R. NELSON, M.D., Ph.D., Director, U.S. Centralized Allergen Extract Laboratory, Walter Reed Army Medical Center

FDA PARTICIPANTS:

GAIL DAPOLITO, Designated Federal Officer
MILAN BLAKE, Ph.D., Director, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, CBER
RONALD L. RABIN, M.D., Chief, Laboratory of

Immunobiochemistry, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, CBER
JAY SLATER, M.D., Deputy Director, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, CBER
VADA PERKINS, CDR, USPHS, Senior Program Management Officer, Office of the Director, CBER

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Adjourn

P-R-O-C-E-E-D-I-N-G-S

8:09 a.m.

CHAIR ATKINS: Good morning everyone. I'd like to welcome you to this meeting of the Allergenic Products Advisory Committee. Since our last meeting, we have a number of new committee members so perhaps it would be helpful if we got introduced to one another.

If we could start with you, Dr.

Plunkett, if you would introduce yourself and your affiliation. And just so you know, these microphones, when you press down, you can talk. And when you let up, they can't hear you. Oh, I can't even get that right.

DR. PLUNKETT: Yes, I'm Greg Plunkett. I work as a research scientist at ALK-Abello. And I'm the Industry Representative.

MEMBER GRANT: My name is Andrew Grant. I'm on the faculty at the University of Texas Medical Branch at Galveston.

MEMBER HAMILTON: I'm Robert Hamilton and I'm at Johns Hopkins University School of Medicine.

MS. FUSCO-WALKER: Good morning. I'm Sandra Fusco-Walker. And I'm with the Allergy Y Asthma Network, Mothers of Asthmatics, Consumer Representative.

DR. NELSON: Good morning. I'm Mike Nelson, Chief of Allergy-Immunology, Walter Reed Army Medical Center and Program Director at Walter Reed National Military Medical Center's new program.

DR. MARTIN: Good morning. I'm Bryan Martin and I'm at the Ohio State University.

MEMBER SHEPHERD: I'm Gillian Shepherd on the faculty of Cornell Medical School in New York or the Weill Medical College of Cornell University.

CHAIR ATKINS: I'm Dan Atkins. I'm at National Jewish in Denver.

And just let me remind you to re-

click your microphone so it turns off. Thank you.

MS. DAPOLITO: I'm Gail Dapolito, Executive Secretary for the Committee.

And I'd also like to take the opportunity to introduce Jane Brown. I think most people met her out in the reception area today. And she's being assisted by Rosanna Harvey, our Committee Management Specialist. Thank you.

MEMBER COX: Linda Cox, Allergist in private practice in Fort Lauderdale.

CDR PERKINS: Vada Perkins, Center for Biologics, Office of the Director.

DR. SLATER: I'm Jay Slater, CBER, FDA, Division of Bacterial, Parasitic and

Allergenic Products.
DR. RABIN: Ron Rabin, Chief of the Laboratory of Immunobiochemistry, CBER, FDA, the Division of Bacterial, Parasitic and Allergenic Products.
DR. BLAKE: Milan Blake, I'm the

Division Director.
CHAIR ATKINS: So I think with that, Ms. Dapolito has a conflict of interest to read to us.
MS. DAPOLITO: And before I read the meeting statement, I'd just like to ask that electronic devices, cell phones, be silenced. Thank you.
The Food and Drug Administration is convening the March 18, 2009 meeting of the Allergenic Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.
With the exception of the industry representative, all participants of the Committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations.
The following information on the status of this Advisory Committee's compliance with federal ethics and conflict of interest

laws, including but not limited to 19 U.S.C. Section 201 and 712 of the Federal Food, Drug, and Cosmetic Act are being provided to participants to this meeting and to the public.
FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws.
Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.
Under 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with

potential financial conflicts when necessary

to afford the Committee their essential expertise.

Related to the discussion of this meeting, members and consultants of this Committee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 U.S.C. 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracting grants, CRADAs, teaching, speaking, writing, patents, royalties, and also primary employment.

For Topic One, the Committee will discuss a proposed change of potency assay for short ragweed pollen and cat allergen extracts from radioimmunodiffusion assay to an enzyme-linked immunosorbent assay. This is a particular matter involving specific parties.

For Topic Two, the Committee will

hear a report from FDA about structured product labeling for allergenic products. This is a particular matter involving specific parties.

For Topic Three, the Committee will receive administrative and research updates from the laboratory of Immunobiochemistry, Division of Bacterial, Parasitic and Allergenic Products, Office of Vaccine Research and Review. There is no conflict of interest screening required for this update.

Based on the agenda and all financial interests reported by Members and consultants, no conflict of interest waivers were issued under 18 U.S.C. 208(b)(3) and 712 of the Food, Drug, and Cosmetic Act.

Dr. Greg Plunkett is serving as the Industry Representative acting on behalf of all related industry. He is employed by ALK-Abello. Industry Representatives are not special government employees and do not vote.

The conflict of interest statement will be available for review at the

registration table. We would like to remind Members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with the sponsor, its product, and, if known, its direct competitors.

Thank you.

CHAIR ATKINS: So our first topic this morning for the Committee is a proposed change of potency assay to be used by CBER for standardized short ragweed pollen and cat allergen extracts. And Dr. Rabin, who is the Chief of the Laboratory of Immunobiochemistry

is going to speak to us about that.

DR. RABIN: Okay, got it. Before we begin with that, I just would like to give the Committee an overview of the laboratory for a little bit of context.

And before I do that, I want to thank the members of the Committee for serving on the Committee and for taking the time to be with us this morning and for giving it your attention and your thought.

I also want to thank the members of the support staff, Gail, for your hard work in putting this together. And any members of the public for their interest in attending this meeting.

The allergenic products that are classified as biologics are managed by the Laboratory of Immunobiochemistry. The Laboratory of Immunobiochemistry is composed of these personnel. My name is Ronald L. Rabin. I'm the Chief of the lab and have been since December of `08. Jay Slater was the

Chief. He, within the context of the lab, has the title of a Supervisory Medical Officer although, as you see, he's -- that's not his only title. The lab also includes Nicolette deVore, a staff fellow, Sandra Mezies, Consumer Safety Officer, Katya Dobrovolskaia, a biologist, as is Cherry Valerio and Aaron Chen, and Mona Febus is a microbiologist with

the lab.
We also have a number of research personnel that are in my research lab. Two post-doctoral fellows, Viraj Mane and Philippa Hillyer. Zeng Zhao is a senior scientist. And two post-baccalaureate research assistants, Ms. Nataly Raviv and Lynnsie Schramm.
We're one of the laboratories within the Division of Bacterial, Parasitic and Allergenic Products or, as I like to refer to it, everything but a virus. Dr. Milan Blake is the Director. Jay has moved from his position as Lab Chief to Deputy Director. And

Jennifer Bridgewater, who is invaluable to us, is the Associate Director for Regulatory Policy and Tina Roecklein, also a very crucial member of the team, is a Regulatory Coordinator.
We work closely with one of the other divisions in the Office of Vaccines, Research, and Review, which is the Division of Vaccines and Related Products and Applications, or DVRPA.
Unlike DBPAP, our division is composed of reviewers/scientists who do have some independent research responsibilities. Unlike DBPAP, DVRPA is strictly a regulatory and review division. Wellington Sun, Dr. Wellington Sun is the Director and Paul Richman is the Chief of the Regulatory Review Branch.
And then we work closely with these Review Officers who are all members of the United States Public Health Service Commissioned Corps, Commander Colleen Sweeney,

Lieutenant Commander Jason Humbert, Commander Joseph Temenak, Lieutenant Commander Michael Smith, and Lieutenant Elizabeth Valenti.
So as I mentioned to you, we have dual responsibilities. Those are regulatory/review and research. And I'm going to just discuss with you our regulatory review responsibilities. I won't be discussing into any detail my research projects. Dr. Slater will be discussing his in a few moments.
So we have routine regulatory activities. And under that category, lot release in which we have, in the last year, reviewed 390 protocols and distributed

reference reagents. In 2008, last year, 2,480 vials and 132 shipments were sent to manufacturers.

We also maintain these reference stocks through semi-annual checks. And, when necessary, we replace them.

Just to give you an idea of the protocols that are submitted, it has been

roughly stable numbers throughout the last decade, anywhere from about 390 to 475 per year.

The distribution of lots, likewise, is relatively stable, somewhere generally between 100 to 150. And the number of vials, again, around 2,000 to 2,500 with occasional dips there but expected variation from year to year.

As we distribute the references, of course, some of our stocks become depleted and they need to be replaced. And last year, we replaced four reference extracts, our cat, Timothy, cat hair, and house dust mite. And one sera, also house dust mite.

This year, we will be replacing a cat sera, actually twice. This is sort of an intermediary lot that we have that we've just validated and are just beginning to distribute. And then because we have that in limited quantities, we are setting up a new lot of serum, new immunization, new sheep.

How do we manage the inventory, we do it through semi-annual reference checks. We estimate the replacement dates based on expiry and consumption. We monitor the manufacturer requests.

We do distribute our sera and reference extracts for research purposes but we can be a little bit stingy with that when we have to be. And so we limit it in order to ensure that we have enough to attend to our primary responsibility.

We have the review responsibilities as well. And that is primarily of an investigational new drug, the IND applications, which are -- these are all sponsor-originated -- or many of these can either be sponsor-originated or investigator-originated.

Sponsor-originated is generally for -- the goal would be for licensure and to

bring to market.
And those that are investigator-

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originated are to use extracts for purposes in which other than they are licensed. So these would be a number of INDs from academic centers in which they might want to use extracts for nasal or bronchial challenges or mechanistic studies. So we review those as well to ensure maximal safety to the human subjects.

We also review Biological License Applications, the initial license for bringing new products to market, supplements, and annual reports.

And then finally, we consult other centers who consult with us when issues of allergenics come up. And mostly that would be the two centers with which, during my tenure here at FDA, has been the Center for Drugs and the Center for Devices.

So that brings me to the second part of my presentation which is entitled, at least on the slide here, the possible change of potency assay for standardized short

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ragweed pollen and cat allergen extracts.

Allergen standardization is defined in the Code of Federal Regulations as we are charged to establish a U.S. standard and to establish a testing procedure. Now along these lines, manufacturers may use the established procedure or they may develop their own equivalent procedure.

There are 19 standardized products amongst the 1,200 or so allergenics. These can be roughly divided into house dust mites, cat, short ragweed pollen, the insect venoms, and the grass pollens.

The unitage varies according to the allergen. For the venoms, it is micrograms of protein based on the activity of the allergenic enzymes.

For ragweed, it is units of Amb a 1 per ml. So that is based on the concentration of the major allergen. And for mite, it is allergenic units and cat and grass, biological allergenic units, BAU per

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ml. And that is based on the correlation of

skin testing to an in vitro assay. And cat is also defined in Fel d 1 units, according to its major allergens.

So according to the standardized products, within the standardized allergens, other than venom, two products can be defined in the United States on the concentration of the major allergen: ragweed and cat.

Now, of course, while skin testing might be the gold standard, we need surrogate assays for the potency. And they vary according to product.

For the house dust mite, it is competition ELISA primarily, for cat pelt and cat hair, it is primarily radial immunodiffusion assay.

Grass is competition ELISA.

Short ragweed, again, radial immunodiffusion assay.

And then, as stated earlier, for the venoms, it is enzyme activity.

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So I wanted to discuss this procedure of radial immunodiffusion assay with you, which we are using currently, for potency measurement of the ragweed and the cat. And to remind you of the procedure for it and why we might consider changing from it.

So the procedure is that the antibodies specific to the major allergen are added to agar. And the agar is solidified. And then wells are punched into it. Equal amounts of the antigen, or the extract in this case, would be added to the wells.

It is incubated for two or three days and then immersed in ten percent acetic acid to fix the diffused extract. And then there is a measure. And then there is a precipitant ring of antigen antibody complexes that is measured.

So just to -- because a picture is worth a thousand words, this is -- these are the slides here with -- I think you can see it on a balance to be sure that everything is

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level with the agar drying.

I had just purchased my camera and didn't realize all the other photos I took that day, I didn't actually snap them. So we're going to skip to the following Monday. And here is the slide being put on the reader here after they have been incubated in the

acetic acid.
And this would be Ms. Valerio who is reading the slide, taking a measurement. This photograph was taken through the slide so this is the agar slide here. You can see the edge here. And this would be the hole that was punched into the agar and the precipitant ring.
And then these two lines are, you know, brought up and measured. And the measurement is taken of the diameter of the precipitant ring.
And then the ring of the manufacturer's lot is compared to a standard curve as shown here. And then there are

standards by which values pass for distribution.
For ragweed really there are no limits or target range. There the vial is simply labeled with units of Amb a 1. And with cat, they are labeled as BAU 5,000 to 10,000, depending upon these ranges of concentration that are acceptable of the Fel d 1 units.
Well, as you can imagine, as you can see, the RID, it works. And we've used it for many years. But it is rather time consuming. It is labor intensive. There can be reader variability. And it is somewhat expensive. It uses a fair amount of serum, antiserum. And it is expensive as well in time.
And so the question, the simple question is: is there a replacement assay that might be quicker or easier that would allow for objective automated data collection, without the danger of subjectivity, I guess I

would say, in analysis that might use less antiserum and other reagents, might be more precise, and give us better reproducibility, dynamic range, precision, and accuracy.
And, of course, like a good lawyer, we don't ask a question if we don't know the answer. So the answer would be that for the most part, ELISAs, or the Enzyme Linked Immunosorbent Assay, fits those criteria.
So, again, just to review for those who are not familiar or who haven't given it a thought recently, all ELISAs have

in common a revealing step in which an enzyme is coupled to a revealing antibody or sometimes it is a biotin-streptavidin pair which converts a substrate into a detectable and quantifiable signal.

That signal may be colorimetric, which is the easiest and the cheapest in both from the standpoint of the chemical and the instrumentation.

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It could be fluorescent, which gives you a broader dynamic range but the instrumentation is more expensive.

Or even luminescent, which is really quite expensive, but it is -- or more expensive certainly, the instrumentation is also more expensive but it is the most sensitive and gives the transient signal.

So we've decided to at least consider a developmental plan for a replacement of these two RID ELISAs -- two RID assays with ELISAs assays. And if, as we choose to do so, we can -- I just want to bring you through the three phases of the developmental plan.

The first phase is proof of concept in which there is feasibility, proof that the test system can work.

Phase two is qualification and validation, showing that the test is stable.

And phase three would be standardization, demonstrating quality

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control, establishment that the test is precise and could be used by different workers in different labs, and availability and interchangeability of non-critical reagents.

So for proof of concepts, we would determine the type of ELISA -- it could be direct, indirect, sandwich, or competition -- evaluate a commercially-available ELISA, which may suit the bill just fine.

And if that's the case, that's all right, or evaluate potential sources and types of antibody, polyclonal, monoclonal, perhaps monoclonal capture, polyclonal reveal, as we consider that a sandwich would be the more likely form that we would use, the antigens, the enzymes, the conjugates, and so on.

So just to bring you through a quick review of these different types of ELISAs, the direct ELISA is the simplest type

where the antigen is passively attached to a plate, to the bottom of a well of a plate, usually a 96-well plate format, the

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conjugated-specific antibody is added, and then substrate is added to develop color.

The indirect ELISA adds some versatility in amplification and here in red are the differences between the antibody -- between the direct and indirect ELISAs.

So, again, here the antigen is passively attached to the plate, the unconjugated -- now you add an unconjugated-specific antibody and a conjugated secondary antibody, which are easily available from many different vendors -- they are very inexpensive -- and a substrate to develop color.

The sandwich ELISA is the most sensitive of these and does not require a pure antigen because in this case, you have a capture antibody that is passively attached to the plate and now the antigen is captured by the plate-bound capture antibody.

And then a second specific antibody, hence the sandwich, is added as

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demonstrated in step three of the little cartoon here. And then a conjugated secondary antibody and then a substrate to develop color.

And the sandwich ELISA requires that the analyte has at least two epitopes, one for capture, one for detect.

So sometimes it is not useful for proteins that are composed of many repeating subunits or for very small molecules. But in our case, sandwich ELISA should be a reasonable approach.

Just to remind you that any of these can be used as a competition ELISA where here you attach -- you bind to your antibody a known concentration of your antigen and then you compete in a solution with your unknown.

So once we've determined what reagents we think that we will be moving forward to, we want to demonstrate qualification. And to do that, we look at precision, inter-assay and repeatability to

determine the acceptance criteria for the validation phase and then specificity as well.

Just to remind you of the definition of precision, which is somewhat intuitive but important to consider what precisely it means, I guess, is the closeness of agreements between measurements obtained by one person repeating a method.

And we can focus on inter- and intra-assay precision to establish acceptance criteria for validation. And this little cartoon really says it the best.

Things can be precise but inaccurate or precise and accurate. So we shouldn't mistake precision for accurately. Precision simply refers to closeness of agreement between measurements.

And, of course, specificity means that you are measuring simply what it is that you wish to measure and not what it is that you aren't measuring -- that you don't wish to measure.

And then once those things are determined, we move to the validation phase in which there is a snapshot of assay performance, of confirmation that the assay performs as we claim and demonstrates that the assay is suitable for intended purposes.

The plan would include a complete list of parameters to be evaluated, minimum acceptance specifications for each parameter, and then describes in detail the steps necessary to evaluate those parameters.

What are those parameters? Accuracy, precision again, and specificity again, detection limit, quantitation limit, linearity, range, robustness, and system suitability.

These are the parameters according to the USP and the ICH for this category. These are different categories of test. The ELISA that we would consider developing is within category one.

And according to the USP and ICH,

these are the things that we would need to address to validate this assay. Again, linearity, range, specificity, precision, repeatability, and accuracy.

So let's remember that accuracy is

a measurement of trueness or bias and is distinct from precision. So in this cartoon, again, these three arrows would be accurate but not precise. And these, of course, are accurate and precise.

So, again, just to hammer this point home, these are accurate and precise, accurate but not precise, precise but not accurate, and neither precise nor accurate.

For validation then, precision is -- inter-assay precision equals reproducibility. Inter-assay variability is within the same lab. And intra-laboratory is really how we define -- is anther way in which we look at reproducibility, the final way.

Now in validating an assay, we need to know what the limit of detection is.

And generally speaking, the limit of detection is defined according to the blank, the measurement of the blank, plus three times the standard deviation of the slope of the line composed of the concentration of the analyte and whatever the signal is.

Above the limit of detection is the limit of quantitation, which is defined not by three standard deviations of the slope but by six standard deviations.

Now in addition to a lower limit of quantitation, of course, there is an upper limit of quantitation. And that is generally determined by the quantity of the substrate in which case, you know, when it is all used up, you reach this asymptote here and also by the ability of the instrumentation to the range of the instrumentation.

So linearity now is where the response is proportional to the analyte added. And the linear range then is the accuracy plus or minus the predetermined variability. So

this just simply demonstrates linearity. As you can see, all the points fall on the slope almost precisely.

But this one begins to fall off. And then this is the linear range here where you have the response over the amounts and then that line should be really -- that should be a quotient, an invarying quotient, and when that quotient falls outside of these 95 percent confidence intervals, that is what defines the limits of the linear range of the

assay.
To continue to define parameters of validation, robustness refers to what one does is one introduces small but deliberate variations to measure the lack of internal influences of the test results.
So, for example, if the assay calls for an incubation stage at 37 degrees, you might incubate it at 40 degrees and 34 degrees to see how that effects the assay or the incubation time or differences in

equipment or even sources of reagent.
Standardization refers to system suitability and generally requires some sort of collaboration. So system suitability tracks and trends assay performances over time and assess the need for re-validation as a result of assay changes.
So, for example, a source of a reagent, a capture, perhaps a detection antibody, or a different vendor for the substrate. And there should be some system suitability check run with each test and then the equipment, reagent, and personnel and procedure are tested.
And then the data are analyzed and demonstrated to meet the acceptance criteria established in the robustness testing.
So in summary, while RID is dependable and reproducible, it is time consuming and relatively inexpensive.
We suggest to the Committee that the ELISA might be a better surrogate assay

for cat and ragweed allergen standardization because it will be less expensive after development, more reproducible, and less time consuming.
And it is particularly in the case for these two environment allergen extracts because they are standardized by the concentration of their major allergen, Fel d 1 for cat and Amb a 1 for ragweed.
And I think that is the end of the presentation, so I'll take any questions or comments.
Dr. Hamilton?
MEMBER HAMILTON: Just one question. Could you clarify again the difference between the limited detection, mean plus three standard deviations at the blank

and what that other parameter was -- the six times standard deviation because I missed that.

DR. RABIN: Sure. So the limit of detection is simply, you know, the limit by

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which you can qualitatively state that something is present but you cannot necessarily measure its level. You can simply say but it is not measurable. The limit of quantitation is that, that you can assign a quantity to it.

CHAIR ATKINS: So are you beyond this phase, I mean where you are thinking about moving to ELISA? Have you already decided how you are going to set that up other than sandwiched? Have you thought about reagents or system?

DR. RABIN: No, where we are with it really beyond -- at this point was simply the discussion phase. We had discussed with -- the possibility of using of -- and we have decided that we would just start with the sandwich ELISA, that seemed to make sense.

And now we're considering what are the reagents we're going to use. So, as we all know, there's a vendor, Indoor Biotechnologies, that has an assay that is out

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that that may simply be the way to go.

We also know that there may be other monoclonal antibodies that are out there. And we, of course, have our own -- we have our own lots of sheep antibody, sheep antisera, including, interestingly, one lot that doesn't work at all for our idea but it seems to work very well in, at least, I think, a competitive ELISA format so it should work here.

And so the question would be whether or not we would want to use one of those for capture and the other for revealing. Or even to use the polyclonal sera, for example, for both, you know, biotinylating, you know, one set of antibody for revealing. Or even to use the polyclonal sera, for example, for both, you know, biotinylating, you know, one set of antibody for revealing.

So where we are is in the design process. But before we even begin to undertake it, we thought that this would be a

good subject for this Committee for either encouragement, suggestions, or discouragement as the case may be, I guess.

Dr. Hamilton?

MEMBER HAMILTON: Personally, I would give a resounding, absolute, positive, positive encouragement to move in this direction. And I would encourage you to consider the two-sided immunoenzymometric assay as the primary target, even though the other assays may work well for the polyclonal antibody.

CHAIR ATKINS: Thank you very much. Do we need to vote?

MEMBER GRANT: I was thinking of what goals I would have as a member of this Committee and certainly improving standardization is something that I would like to see. The radioimmunodiffusion was what we were doing four decades ago. And it has the same limitations now. So it clearly has outlived its utility.

And it would be nice to see some uniformity across the allergens as we begin to expand the small panel you have into others to really make diagnosis and treatment more effective. So I applaud your moves.

DR. RABIN: Thank you.

CHAIR ATKINS: Dr. Nelson?

DR. NELSON: Thank you. Great presentation.

I wonder if you would comment on the timeline for developing these validation processes, both from an in-house development from scratch and those for us utilizing one that is off the shelf.

DR. RABIN: That's a good question. Having never actually done this process, I'm a little bit hesitant. Sandy do you have -- if I can just direct the question -- oh, Jay, Dr. Slater?

DR. SLATER: Yes, hi. It is a very good question. It's -- what Ron described would be his process as the Lab

Chief within the group of going forward with this.

But he also described a sort of tricky part of validating the assay. And the other part that he mentioned but didn't really

go over in great detail is that typically most of the manufacturers have adopted our assay approaches even though they can try to put equivalent assays into their license applications.

So the fact that we're switching or we're thinking of switching from one assay to another doesn't obligate the manufacturers to do so.

That being said, this is a workhorse assay for extracts that our manufacturers make a great deal of. And so the manufacturers actually test for Amb a 1 and test for Fel d 1 on a very regular basis. It is a relatively high-volume activity for them.

Therefore, our interaction with

the manufacturers will probably be an important part of this. And that can also effect the timing.

So whereas what Dr. Rabin described arguably could be done in six months, nine months, my guess is that the process, because it is more of an iterative process and a cooperative process between us and the manufacturers, may take longer.

I don't know if Dr. Plunkett wants to comment on that.

DR. PLUNKETT: Well, no, I think -- I mean I agree with everybody. We have experience in our lab with at least the Fel d 1 assay. And, you know, we've gone through a lot of these validation steps ourselves. And I don't see it as being something that, you know, would be overwhelming at all.

DR. SLATER: But I guess my point was that in addition to the science, there is also a regulatory component. The manufacturers, if they do wish to switch to

our assay, are going to have to submit supplements to document that and to show that they are actually capable of doing the assay, hopefully as well as we are.

CHAIR ATKINS: Yes, Dr. Shepherd?

MEMBER SHEPHERD: What is the data on the percent of patients taking ragweed that have IgE to the major determinant versus some of the other minor ones? Or cat? Does anyone know that?

My concern is just that we now

have a system that obviously can be highly standardized, which is great, with the major antigen and also a monoclonal to that. But in a biologic system where we're now giving these extracts to patients, many of them have antibody to other determinants.

And is there any -- you have a very narrow system here but you are missing, perhaps, patients that might be very sensitive to some of the other determinants. Can you consider periodically either also setting up

an assay for some of the minors and/or periodically using sheep or other antibody that is broader just to see what else is there?

DR. RABIN: Well just to clarify, in the current instance, the assay is for the major antigen now. That when -- the sheep sera, the sheep are not immunized with a crude extract. They are immunized with the purified major antigen.

As to the variation in the human response, I am going to direct that to Dr. Slater.

DR. SLATER: Well, you know, you're obviously asking a good question.

With the ragweed, we know that the percentage of individuals who have their primary response to non-Amb 1 allergens is actually quite small. And, again, as Dr. Rabin said, we actually don't have any way of picking that up in the extract now because we don't use pooled human sera. We actually use,

you know, a specific sheep antiserum.

In the case of cat, as you well know, cat albumin is an important allergen in a substantial minority of cat-allergic individuals. We actually don't have a quantitative assay for cat albumin at this point.

We do have a qualitative assessment for the presence of cat albumin in the cat pelt extracts, which was on the table that Dr. Rabin showed, and it is a critical part of our evaluation of those extracts.

One of the sort of unspoken attractions of the direction that Dr. Rabin would like to take these assays is that while we're doing this, we might possibly be able to quantify the presence of cat albumin in the

cat pelt extracts.
That would be a large change. We're not saying we're going to do this but technologically it would be something that Dr. Rabin and his group could address in their

assay development that would actually be attractive and possibly advantageous.
DR. PLUNKETT: In the development of the ragweed assay, have you considered whether or not you could develop one that would be cross reactive with maybe the giant ragweed equivalent or homologue, the Amb t 1?
DR. RABIN: No, we haven't. We haven't to date.
DR. SLATER: Should we?
DR. PLUNKETT: Well, the amount of -- just from extract sales, I could say that we probably sell a large amount of giant ragweed. In fact, one of our common products is a ragweed mix.
So the RID method, as you know, does not react at all with giant ragweed even though there is probably the homologue antigen. I was just curious. If you are screening antibodies or whatever, if you had thought of doing something like that?
CHAIR ATKINS: Dr. Cox?

MEMBER COX: Jay, Dr. Slater or Plunkett, when we were updating allergen immunotherapy practice parameters, we did discuss giant ragweed. And with the advice of one of our senior members, Dr. Len Bernstein, apparently there is very little evidence that giant ragweed is a significant cause of clinical allergy in the United States even though there is a paper coming out of Italy that looked at differences in allergenicity.
But it didn't actually address the clinical issue of whether these people failed immunotherapy because they didn't have giant ragweed in their allergen extracts. So I guess I don't think it is important, that's what I'm saying.
CHAIR ATKINS: Yes, Dr. Grant.
MEMBER GRANT: Well, I certainly think that attention to cat albumin would be worth considering because it does seem to have a reasonable role in the allergen spectrum of people.

What is the latest figure for individuals who are ragweed sensitive that might be sensitive to minor? Is it Amb a 5 that is one of the more important ones?

DR. SLATER: I don't know the answer to that.

MEMBER GRANT: I remember when we thought that Amb a 5 had no importance whatsoever and I spent the night with a patient who had anaphylaxed to the testing and the patient did survive but it certainly showed us that there are individuals that are extremely sensitive to minor ragweed antigen.

So I'm just wondering if some attention needs to be directed when one is comparing one manufacturer to another. Amb a 1 is most important as Fel d 1.

DR. RABIN: Thank you. We'll consider that.

CHAIR ATKINS: Would measurement of these minor -- I mean this starts to effect the cost of the extract and the availability

of extracts, correct? I mean that's part of problem. If we start looking at a variety of different allergens and standardize these further, is that the concern?

DR. RABIN: Yes, I think that would be the concern certainly of changing the parameters of standardization. I think that, you know, that is an issue. Perhaps something straightforward -- to simply know, cat albumin might be worth considering. But to change a parameter of standardization would be a very major issue.

CHAIR ATKINS: How long do you give industry to catch up? I mean is that something you would negotiate in discussions with them? Or I mean once you set the standard, how long do they have to comply?

DR. RABIN: Well, I think that our sense is that if we go with a sandwich ELISA with a colorimetric revealing system that this is something that all manufacturers, they have the technology, they have the reagents.

And, of course, as the final part of the validation, they need to demonstrate that they could reproduce it. If it is a robust assay, that should be the case.

Once it is all demonstrated that

it could be reproduced and we're all comfortable with it, I think that we would move forward with it.

CHAIR ATKINS: Any other questions for Dr. Rabin?

(No response.)

CHAIR ATKINS: Thank you very much.

I think we're running a little ahead of schedule. So maybe on that note, rather than take a break, we could move to a discussion of the structured products labeling. Vada Perkins is going to talk to us about that.

CDR PERKINS: Can everyone hear me? First of all, I'd like to thank Dr. Rabin, Dr. Slater, and Gail for this

opportunity to address this panel.

What I'm going to talk about here is well, as you can see, a structured product labeling. One of Dr. Rabin's slides had alluded to the process of how we review applications, the content of labeling associated with products.

So there is our original application process along with the supplements, and annual reports. Within those reviews related to labeling, a lot of the most important information that practitioners have access to would be in the package insert.

So the evaluation for efficacy and safety in a product would be captured in that package insert. And, therefore, practitioners would be able to access that information and to determine what is the best medication to provide for their patients based on looking at that information.

Currently -- well, in the past, that process was paper. So we would receive

something in paper, review it in paper, send faxes back and forth, company would receive that. And then you would finally see something in crinkle paper or in some other medium.

Over the last few years, we've had those negotiations come in electronic format, Word documents. Label negotiations go back and forth. And then ultimately we would send that information back to PDF.

You would either find it, like I

said, in the package insert, the paper, or possibly a company might post it on their website in PDF or you might find it on the FDA website.

What we've come to find out is that there really isn't a one-stop shop repository for locating package inserts or information on products. And additionally, that information really isn't accessible for other things such as data mining, adverse events, or for pharmacovigilance in any

format.

So with the initiatives that you probably heard about with President Obama, health IT initiatives for having e-health records, things of that nature, this really supports that initiative because this presentation is going to cover basically how we're going to code the information that is contained in a package insert with control vocabulary from various terminology maintenance organizations.

And to be able to put that information in a format that if, in the future, someone has some type of database they want to use for adverse events or some pharmacy wants to use it, or if you do have, in the future, electronic health records, you would be able to take the information associated with these products and maybe bounce against it for contraindications or any other type of -- I heard someone discuss today about sensitivities to products.

What we're trying to do is to code active ingredients within all of these products so that you, in the future, would be able to use this information to better serve your patients.

So just a bit of background on this, this is actually way in advance of what happened with President Obama's decision for the 50 billion dollars, I think, for e-health records.

Back in 2003, the FDA had published regulations requiring that content of labeling be submitted electronically in a form that the FDA could process, review, and archive. Some of what I told you, some of the limitations we had before with paper submissions for content of labeling not being

available to practitioners or to the public pose a huge problem for us.

So the Center for Drugs had announced in one of their public dockets that they were only going to accept electronic

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submissions of content of labeling effective October 31st, 2005. They weren't accepting PDF anymore or Word versions for us to review. And they needed to put it in a format that, as I mentioned before, that was coded and the information could be accessible later on in other database forms.

And that's what we're calling SPL. And I'll get into some more detail about what that is exactly.

So three years later, the Center for Biologics decided that we were also prepared to do that with our products. And we are going to be doing that for original submissions, supplements, and our annual reports.

So now we're getting into the meat of the presentation. So what is structured product labeling? Structured product labeling, in essence, is extensible markup language. We're using a Health Level 7, which is basically a standards organization, to

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create machine-readable tags to improve search functionality across various systems with our package inserts.

The whole purpose of that, of course, is for usability across multiple database platforms. As I mentioned before, if, in the future, someone decided that they wanted to develop some type of improved adverse event reporting system or they wanted to use it for data mining for some other reason -- research -- they would be able to have access to this information instead of having to manually input whatever they were trying to develop.

It would enhance search capabilities and, of course, as I mentioned, promote electronic health information initiatives such as e-health records.

In the current state, as you can see, readability, crinkle paper, very small, accessibility to package inserts, trying to find information is very difficult at this

time. And, as we mentioned before, usability -- paper labels and forms cannot be accessed by computer systems. You can't scan them. Even if you were able to put it in a format where you made that text searchable, you don't know from one scan to another what you are getting.

So we need to have some type of controlled environment to be able to take this information, control the vocabulary and the terms, and make it usable in the future.

This is a representation of what you are currently working with or what people normally see, small package inserts. Alternatively, our drug registration and listing system, companies have to register their establishments and their facilities once a year. And they have to list their products with us twice a year if they have changes.

That's also paper as well. So if there was a manufacturing change or there was some other change in their product that wasn't

reportable to us by regulation for that year, this would come in this paper form here.

And what happens now is all of this is manually taken out and someone is manually entering it into a system. So it's not very good for us because there is no way for us to validate this information. Same thing with content of labeling.

This is basically a representation of what structured product labeling is. Don't get caught up with too much of the details. What is in your package insert, what you see, is going to be the same presentation you see for your physician labeling rule, your package in front of you.

Behind the scenes for the way we are receiving this in SPL, you are going to see all of this coded information. This coded information are the machine-readable tags. Within these tags, we're coding active ingredients, inactive ingredients, units of presentation, dose forms, routes of

administration, things of that nature.

So for the practitioner, you don't have to concern yourselves with what is behind the scenes. What you are going to see electronically in your presentation is exactly

what you see in your paper package insert and content of labeling. It's just going to be a lot of information behind the scenes that is coded for future use later on when we determine a better use for it.

By putting it into the structured product labeling format, as I mentioned before, it is going to improve accessibility. It is computer readable. And we can import this type of information in this XML format into different systems. Plus it makes it publicly available.

As I mentioned, the biggest issue we have right now is that if you were to go and say I want to find one resource where I can find all of the package inserts for the products that the FDA approves, you probably

wouldn't be able to find that anywhere.

And then if you did find something that sort of met that need, you would really be able to do anything with that data to better serve you to make a decision without going to each product -- each PI by itself.

So, for instance, if you were trying to find products that had peanut oil in it, you know, how you would go about doing that search right now might be fairly exhausting. But if you've coded all of that information, you have a code for peanut oil and it is controlled, by having all of this information in the future, then you should easily be able to determine what kind of ingredient that you are searching for.

All of this piece here is just basically trying to let you know whether or not this is something that is mandatory or is this something that is recommended. So this exercise that we're embarking on would be very, very difficult if we didn't have buy in

from industry.

So this is something that is mandatory, that pharma will have to adhere to. We put out a draft guidance for industry July 11th, 2008. And it was a voluntary program.

We basically said right now you are still doing this all in paper. We have a system in place where you could provide this to us electronically. Please participate because in June of 2009, per the new regulations, you are going to have to do this

anyway.

So it's been -- I would say pharma has been pretty receptive. We've had a lot of buy in from a lot of them. We've done a lot of outreach. We've done some public workshops, a lot of webinars.

We've tried to work with companies one on one to get them up to speed so that by June 2009, all the information that we receive from these companies regarding the package inserts, the content of labeling and their

registration and listing information would be entirely electronic so that we can put it in this format and eventually provide it to the end users, the patients, the health care practitioners to view this information however they choose.

None of this information would really be of any benefit if we couldn't validate the information somehow. So not to get caught up in all the details of this diagram but this is just a representation of how we're going to validate this information. And I'll explain.

So if someone were to submit something to us electronically, and let's just say it was in PDF or in Word, we really would have no idea whether or not that information was accurate without reviewing this information first.

So, of course, time is of the essence. We have a limited portion of time to get through a review. But we already know

that there are certain things that we care about that if we could just make that automatic when it comes through an electronic system, we wouldn't have to worry about reviewing it. It would automatically reject it.

So within this validation process, we have approximately 750 validation procedures built in.

As I mentioned before, it is important that when somebody provides information on their product that the ingredients are correct, that their national drug code, their NDC is correct so that we know it is that company, it is that product, it is that package. It is important that the route of administration is correct, all of

that information.
Since it is control terminology and it is coming from a terminology maintenance organization and it is all coded, the codes are the same. So when someone

submits this, if, in fact, there is an error with what they have submitted, it doesn't go through our system. It will invalidate it. It will actually go back to a company and we'll say your active ingredient is incorrect for this product. The route of administration that you have put in here is not right.
And, therefore, they would fix that. They would resubmit it. And once they have passed all the validation procedures, then it would come to our system. And then it gets posted on a website, which I'll go to. It's on the National Library of Medicine's DailyMed website.
In the past, there was also no way to associate the content of labeling with the manufacturing or the listing of that company. So those were two separate areas.
A company would get their product approved. They would provide the content of labeling that you would find from the review process. But there might be some

manufacturing issue that is going on with that product. And you might want to know about that.
Because this is all electronic now, this is just a representation how we are tying in the NDC number that the company's have, the establishment numbers, the manufacturing operations in those establishments, and that's all being tied into the content of labeling.
So the benefit to the public as well and to us for validation -- this is a validation piece as well as that. If someone submits content of labeling, it is going to tie into their registration. If they tell us that the manufacturing operations where they make the product doesn't match up with when they listed it, it is going to fail validation.
If they tell us that their facility where they make this is in a location -- let's just say that it is in Pennsylvania

and then when they list, they say it is in New York, well that is a problem for us for our folks in compliance and inspections. And that really puts us at a disadvantage about knowing exactly where they are manufacturing this product.

Because all of these systems are now talking to one another because of the way the content is coming in, it will invalidate that as well. So everyone has heard about what was going on with the whole heparin piece and different facilities, something like this, had we had it say a year, a year and a half ago, would certainly give us more information to possibly have prevented something like that.

I might have -- let me go back -- here is what I want to show you. So okay, that was a whole lot of discussion about, you know, what is the end game, what is the benefit to you?

So when all of this content of

labeling comes in from the manufacturers and it is listed, you really don't care too much about that. What you care about is what is the benefit to me.

So when it comes through our system and has to go through those validation procedures -- so it actually has to come through the FDA. We have to look at it and make sure that it is okay.

And we have an agreement with the National Library of Medicine now where once that content of labeling comes through and it passes validation, it automatically gets posted to this website so that health care practitioners or even the public can go back and they can look this medication up.

Let's say, for instance, you prescribe the medication to a patient. They don't have their package insert. They say, you know, it says on the bottle -- I'll put Ambien -- as if this presentation didn't put you to sleep already, I'm going to go ahead

and look up this product here.

And you'll see Ambien. You'll click on it. And it will provide all of the information.

Now, as I mentioned before, this

came through the FDA. It is the only way this information gets posted. So we would have already validated this information saying that it was correct.

Then you'll see all of the information that you need. At the bottom of it all, what we have are called data listing elements. All of this information is what we have coded behind the scenes.

So you want to know about the packaging, you want to know about the ingredients. And I'll just scroll up a bit here. You'll see all of the ingredients associated with this product.

And, as I mentioned before, all of this was coded. If you wanted to know about let's just say this lactose, you just wanted

to know, you know, what other products contain that, you could search on that once we get all this information from the companies and it will give you that representation. Here are all the products.

I want to know if this product contains thirmerosal. You know you can do that and it will just give you a list of all of those products.

So I'll close out of this. Okay.

With terminology, as I mentioned, only control terminology is permitted. And we have that built in validation.

So someone can say my route of administration is intradermal. Someone can say it is subcu. There is a code associated with that. That code is going to be the same for everyone. So it doesn't matter what product that they are using.

And when you scroll down here, what we have our manufacturers looking at is that when they give us that information, it

actually bounces against this list that is in here. And you'll have a whole list of routes of administration, package types, color, shape. That doesn't effect us but that information is here. And we update this every month so we have the most current information available.

For the biologics, and specifically the allergenics, what I can tell you is that, you know, since these products are much different than an Ambien or other

small molecules and chemicals, chemically-structured products, we have to create hierarchies for our products in biologics.

They are much more difficult to characterize and they're complex. So that requires a lot of work with the gentlemen you see sitting over here, our subject matter experts.

When we're trying to code active ingredients for allergenic products, we have to go to our experts to give us that

information. And once we get that information then, like I said, you would get this code. And you would be able to access all this information.

And we're trying our best by June to provide all this information to the allergenics industry so that by June when you provide your labeling, it would be available to the general public on this website.

The Data Standards Council website, I merely just put this here if anyone was ever interested in looking at not only structured product labeling but if you were interested in individual case safety reports or any other bioinformatics initiatives that the FDA is engaging in, you can go to this website and it will give you all of this.

Structured product labeling really is really something that we're using to support individual case safety reports as well. I think that is where it initially started.

We want to be able to take information from post marketing, tie it in to what we are capturing in products, and use that for adverse events.

But we're finding out later on with health records coming on electronically that there are going to be many more uses for this information. And probably other uses that we haven't even identified yet that you might find a need for in the future.

Lonnie Smith and Dr. Randy Levin actually work for the Office of Critical Path Programs. They are on the Data Standards Council. They are an integral part of trying to get all of this initiative passed through. And I just want to acknowledge them here.

I apologize for rambling. It's 30

minutes to probably discuss something that we've taken months to go over. And we still haven't figured out everything.

But I thank you for your time. And if you have any questions, I'll take any

questions.

CHAIR ATKINS: I didn't notice any rambling. I thought that was very concise. Thank you very much.

Are there any questions?

Dr. Hamilton?

MEMBER HAMILTON: I have just one question. What is the -- do all ingredients have to be listed? Or is there a percentage above which they have to be listed? In other words, impurities, things of that nature.

CDR PERKINS: Well, that is something we have been discussing for -- well, for active ingredients, all your active ingredients have to be listed. And we're coding those pieces now.

As far as your inactive ingredients, those currently, by regulation, are only recommended. You don't have to submit that information. But in the future, of course, to make this system more robust, we want to have those active ingredients.

So if we're talking about adjuvants or we're talking about a few other things, excipients, we have to make those determinations. And we're still discussing those.

You know, for example, if there is something that is not a sensitizing agent, do we really want to capture that inactive ingredient? Probably not. But if it is a known sensitizing agent, maybe we want to capture that and code it.

So we still have to work out the details with that but to answer your question, in current state, active ingredients you do have to list but the inactive ingredients, you don't.

MEMBER HAMILTON: The only reason I asked that question is when we had adverse reactions to Xolair, it was the impurity that really ultimately gave us the clue as to what might be going on with some of the individuals who had these reactions.

CDR PERKINS: Well, I wouldn't say that in the future, we'll probably have to look at those case by case. That's sort of what we're doing now.

In those instances, if we do identify something that -- in that particular case, we would have to take that into consideration. Otherwise, it does defeat the entire purpose of using this information for adverse events and for pharmacovigilance.

So I would say that we have a lot of work to be done. I think we've started with the actives. We're going to go with the inactive ingredients.

And I think in the future from what we receive in case safety reports and what we receive from our staff at the FDA and what we receive in reporting in general from MedWatch or from AERS or VAERS, we'll have to take those into consideration.

And if we see those types of ingredients or we see something like that,

we'll certainly have to code that and capture that.

CHAIR ATKINS: Dr. Cox?

MEMBER COX: I would echo Bob -- Dr. Hamilton's comments that the inactive ingredients are important. These issues come up actually not infrequently in the clinical practice, the adverse reaction being to other than the active ingredient. And that was a comment.

And a question is: is this currently available on the web? That we can research or access these --

CDR PERKINS: You can't actually -- I'm glad you asked that question because I --

MEMBER COX: Because I haven't see it when I --

CDR PERKINS: Right.

MEMBER COX: -- I get Medscapes but I have not seen this site come up when I go searching --

CDR PERKINS: Right.

MEMBER COX: -- for, you know, medication.

CDR PERKINS: Well, that's a good question because that was going to be my 31st

minute, you know, but I only had 30 minutes.
Currently there about 4,400 package inserts on the web. In order to get on the web, as I mentioned before, with all those validation parameters, we want to ensure that we've captured all of that information and that it is accurate before it goes on the web.
The one thing that we were working with in our biologics domain is that we have to code these ingredients. You know for the small molecules, like you said, they just take the chemical structure, they post it up there. That's done for them.
We're still coding our products. And as they get coded, we're passing that information along to industry. And then

they're posting that. They're listing it and it is getting on there.
So I would say by June, you would probably see a lot more biologics on there. We probably have about maybe ten to 15 that are there now. But June 2009 is our cut off date. Well, that's the mandatory date for doing this electronically. So you will see more.
But right now, you're right. It's not a one-stop shop resource. But the goal is that it will be sometime in the near future, within the next year or two.
CHAIR ATKINS: My impression is this is reformatting information that we get now. You're not requesting more information from people at this point. Is that correct?
CDR PERKINS: No.
CHAIR ATKINS: It is what is going to be in the usual package insert. You're just putting it in a different format that is searchable --

CDR PERKINS: Right. So right now if you noticed there is a non-PLR format when you see it. And we have our physicians' labeling rule for some of the other ones. So that's the whole half-page presentation that you see.
In current state, we have not changed any of that. This system, these forms -- and they are available for free -- I didn't go into that level of detail -- but it takes into account that.

So we're not asking for anything new other than what is currently required by regulation to submit to us. And if someone has a PLR-formatted package insert, they can click on that and it will automatically format it for them in that current presentation.

CHAIR ATKINS: Thank you.

Dr. Grant?

MEMBER GRANT: I think this is an incredibly useful activity, that having a multiplicity of different inputs is very

irrational. And the one you've chosen looks like it is in the public domain and will not be susceptible to copyrights and patents that would interfere.

You were speaking about the minor ingredients. This comes up in my practice all the time, that we have a reaction to a drug, usually in the in-patient setting.

And we really need to know as much about the contents of the product that we can so that we can try to search for a solution for the patient to avoid or otherwise be managed properly. So I would encourage you to try to get as many things into the database as you can.

With allergenic extracts, we really don't know what is the most important. So we were speaking in the previous presentation about just two proteins.

And clearly it would be ideal to have as many of the minor allergens quantitated and listed in these presentations

as possible so that we really would have that information.

So very good job.

CDR PERKINS: Well, thank you for that comment.

I just want to clarify something. With the inactive ingredients, we are going through the exercise of coding those. It is just that right now manufacturers aren't required to submit that information to us when they list their products.

In the future, that might change because of what we're trying to do here in the interest of the public. But that's why I put my e-mail address here as well. If you have any questions, comments that you would like to -- or examples, as you've mentioned, please

feel free to send me an e-mail and provide that information.

You know all of this in is its infancy. You know we are in a pilot stage with some of this information. We're trying

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our best to see what we can do in the interest of pharma and for the health care practitioners and the general public.

So if we're, you know, if we're missing something or if there is something that you want to make sure that we're capturing, please feel free to e-mail this to me and I'll certainly pass it forward to our folks so we can do our best to capture your concerns.

MEMBER GRANT: Thank you.

CHAIR ATKINS: Yes, Dr. Martin?

DR. MARTIN: I had one additional question. I mean it really is going to be an incredible resource.

Are there going to be any images on it?

CDR PERKINS: There are. And thank you for asking that. There is an initiative right now -- and actually it is through the National Library of Medicine -- where they're going to take pictures, high

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level, high resolution images of products.

And, of course, part of that is so that patients have questions about which medication to take because they were prescribed ten medications, if they want, in fact, to be able to look at an image of a pill, so to speak, they will be able to go into there.

So part of this initiative is to have images in there. Or to have images in there for all of those products.

That is correct. For biologics, of course, in terms of vials, you know, we haven't really talked about that. But certainly for the pill forms, you know, those forms, there is an initiative there to take those pictures and to have them posted and available as well.

All right. Well, thank you very much everyone.

CHAIR ATKINS: Thank you.

Now that we're -- we're still

ahead of time but maybe we can take a 15-
minute break now and then group for the open
public hearing. Thank you.
(Whereupon, the foregoing matter
went off the record at 9:26 a.m.
and resumed at 9:50 a.m.)
CHAIR ATKINS: We'll go ahead and
get started. There may be people who are
planning on coming to the open hearing. And
it was scheduled for 10:45.
So rather than start with that
earlier and inconvenience people who might
have wanted to say something, Dr. Slater has
agreed to give his presentation now about an
update on research of the program.
DR. SLATER: Good morning. And I
want to reiterate what you've heard already
from all of us. And that is thank you for
coming and thank you for participating and
joining us and learning about our program and
some of our initiatives.
I have possibly the easiest and

happiest job and that is that I'm going to
actually review the research activities of the
Laboratory of Immunobiochemistry.
And it is easy because it's, I
think, very good, productive, important
research. It's research that in many ways
nobody else in the country does that needs to
be done. And I get to brag based on other
people's achievements.
I'm going to talk about our
projects. I'm going to talk about our
publications. And I'm going to brag to you
about the kind of support that we get within
the FDA and why we're in such a terrific
position in terms of our research activities.
Now I'm not going to go into great
depth about Ron Rabin's research activities.
I'll let him cover that at the next Advisory
Committee meeting in the next year.
But Ron has been with the lab now
for eight years. And he's got a very
sophisticated and very successful program

going on in terms of characterizing innate
immune responses to respiratory syncytial
virus, which, as you know, is really critical
to understanding not only the allergic immune
response but also, we think, in terms of the

success or lack thereof of allergen immunotherapy.

And so his work is really basic and critical. But I'm not going to talk about it any more because it's not my work.

I am going to talk to you about the two projects that I have been pursuing for the last several years in terms of looking at endotoxins and dust mite allergen extracts. And also the development of a novel potency assay that we think is possibly going to help us out in the years to come.

So the first project I'll talk to you about -- and for those of you that were at the oral abstract session on Monday afternoon at the Academy meeting, I apologize. You will be seeing many slides that you saw already.

But you'll be seeing some slides that you haven't seen either.

The first project is bacterial endotoxin and DNA in house dust mite cultures and extracts. And the person that has been doing most of the work in this is Cherry Valerio in our lab.

But we've also had some work from a medical fellow from NIH, Bhavini Trivedi, many years ago who helped us out, Larry Arlian from Wright State University, and Pat Murray from the Clinical Center have also contributed in critical ways to this project at various times.

The initial studies, which we actually published in 2003, were really in many ways repeats of studies that had been done over a decade earlier in the lab in the hands of my predecessors. And that was that we found, once again, that endotoxins were present in many standardized allergen extracts.

This is not surprising. We've known about it for many years. It is an intrinsic part of these products. And there's no reason to believe that it adversely effects the safety or efficacy of the products.

Nonetheless, because we know that endotoxins are active immunologic agents, we were interested in characterizing this and defining this better, especially with the current generation of standardized extracts.

And some of the things that we

found didn't really surprise us all that much. We found that cat and dust mite extracts had significantly more endotoxin in them than the pollen extracts, which really contained relatively little.

Within the cat extracts, we found that cat pelt extract had more than cat hair. But what we were totally surprised about and didn't really know what to do with was that we found that D. farinae mite extracts had significantly more endotoxin than D.

pteronyssinus extracts.

And when we first did this experiment with a half a dozen extracts, we thought that this was just accidental. But we pursued this and kept assaying extract after extract and we found a very dramatic pattern -- really as much as 100 to 1,000 times as much endotoxin in the D. farinae extracts as in the D. pteronyssinus extracts.

So this was something that we felt we needed to investigate. And we secured a source of live mite cultures. And suffice it to say that we tried many methods of actually culturing bacterial out of these live mite cultures and failed.

So we went to a second approach. And that was to look for bacterial DNA sequences that were present in these live mite cultures. And that was actually fairly straightforward.

You are able to extract genomic DNA from fresh, extensively washed dust mites.

We were able to amplify specific bacterial 16S ribosomal RNA sequences in that genomic DNA from the dust mites.

We were also able to quantify it using internal standards that we developed and I'll talk about a little bit later, sequence it after -- sequence these sequences after high-fidelity amplification, and attempt to identify the predominant organisms.

And this is from one of our earlier experiments where we were able to extract a DNA from both D. farinae and D. pteronyssinus. And you can see here there is no real difference between the amount of DNA that we are extracting.

That's not surprising. The D. pteronyssinus mites have their own DNA. And

we were able to actually show that it was EcoR1 digestible so that was reassuring as a first step for the extraction.

And then when we went back and amplified this DNA, however, we started to see

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some qualitative differences and these are amplifications using specific bacterial primers that have been studied and published ten or 15 years earlier.

What you can see is that we find sequences at the predicted size of 1,800 base pairs in almost all of the mite extracts we looked at. And there seems to be some greater signal from the D. farinae than from the D. pteronyssinus.

So we constructed internal sequences with a -- that would be amplified by the same primers but with a lower molecular weight. We constructed them. We amplified them. And we quantified them with great precision. And then used those to spike our amplification mixes and to attempt to actually quantify the number of copy numbers that were present in each of these.

It's a fairly basic way of attempting to quantify the number of copy numbers that we were starting with. And what

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we were able to do was construct good dose response curves.

We were able to identify where our internal standard was amplifying in each of these runs. And then we were able to estimate the number of copies per nanogram of bacterial DNA that was present.

And you can see here that in our D. pteronyssinus extracts, we were able to quantify -- the absolute number doesn't really matter -- about 77 copies per nanogram of genomic DNA. Whereas in the D. farinae extracts, there was substantially more -- about 1,000 copies per nanogram of genomic DNA.

When we then went back and analyzed these sequences, we found a whole number of different sequences that were present. And we reported this in 2005 with a predominance of many different alpha-proteobacteria, some of which had been identified as endosymbiotic bacteria in other

kinds of insects and mites but many of which we could identify as various Bartonella species.

Rarely we identified other gram negatives. But for the most part, we were identifying other Bartonella species.

And at first this surprised us but after some further examination, we actually found the Bartonella had been identified as a symbiotic organism that is harbored by many other small, crawling creatures, lice, fleas, tic, and certain flies.

Just to review because I certainly didn't remember this, these are gram-negative rods that are facultative, intracellular, and very hard to grow, which explained our failure to grow them initially.

And, again, to review things that I needed to review and you might not be remembering right now, Bartonella-associated diseases are actually fairly common, the most common of which is cat-scratch disease, which

is caused by Bartonella henselae. However the louse-borne diseases have been historically terribly important.

Fortunately, trench fever was not uniformly fatal. It was fatal in malnourished, otherwise injured individuals but hundreds of thousands of soldiers in World War I died of trench fever that is cased by B. quintana. A modern form of trench fever occurs in the homeless individuals that are louse infected and can be seen in many cities in the United States.

Bartonella bacilliformis causes a disease called Oroya fever in South America. Oroya is the name of a town in Peru where this was described. Carrion is the name of the Peruvian medical student who infected himself with the disease intentionally and achieved posthumous fame because of that.

The milder form of the disease is verruga peruana, which is a wart from which Dr. Carrion extracted the material that he

inoculated himself with intentionally.

And then there are a number of diseases of uncertain transmission that have been enhanced with the HIV epidemic. Bacillary angiomatosis is now known to be

caused by B. henselae and B. quintana as is bacillary peliosis hepatis and many cases of culture-negative endocarditis.

Fortunately, there is no evidence of iatrogenic infection. We know that our mite cultures are sterile. But we were concerned that we really didn't quite understand what was going on here and why there was more Bartonella in D. farinae. And so we wished to take this a little bit further.

So the next questions were we know that endotoxin is immunologically active. We also know that bacterial DNA sequences are immunologically active. And we wanted to know whether these sequences were actually detectable in the extracts themselves.

And then because we were looking forward to the possibility that we might wish to reduce the amount of bacterial DNA and endotoxin in these extracts, we wanted to know how widespread a phenomenon this was.

So we wished to look at whether these same sequences could be detectable in other mite species, not necessarily D. farinae and D. pteronyssinus. So we'll talk about that for a few minutes.

To look for DNA in the commercial allergen extracts, we had to use a different method. DNA all was too low sensitivity to actually work. So we used QIAamp resins, with which we were able to actually concentrate the DNA about tenfold. We then did PCR using the same primers and did sequence analyses as well.

And what you can see here is that we looked at many different allergen extracts. We looked at 13 D. farinae extracts, 14 D. pteronyssinus extracts, a couple of cat hair

and cat pelt extracts, three roach extracts. And just to be thorough, we looked at a couple of pollen extracts and a honeybee venom extract.

And just looking at whether DNA was detectable at all, you can see that we detected DNA in the overwhelming majority of our mite extracts, 12 out of 13 or 12 out of 14. And interestingly enough, we detected DNA in two out of three of the German roach extracts. But we didn't really detect any DNA

in the cat, pollen, or honeybee extracts.
When we looked for bacterial DNA using the specific bacterial, specific primers, we found, in this case, that the 16S RNA sequences were present in, you know, between a third and a half of the D. farinae extracts and none of the D. pteronyssinus extracts in this particular experiment, which is different from what I showed you before, in one out of the three roach extracts and in none of the other extracts.

Let's see, did I skip it? Yes, I actually don't have the slide here that shows that the sequences that we identified in these were predominantly Bartonella, as before.
And then looking at the non-dermatophagoides mite species, we looked at C. arcuatus, L. destructor, A. siro, and T. putrescentiae, which are storage mites, and E. maynei is a house dust mite that actually is present in U.S. households as well but it more studied worldwide.
And in this case, we could go back to our old method of using DNAzol, amplifying, and then analyzing the organisms. And here you can see that first of all from T. putrescentiae, even though we identified a significant amount of DNA -- of bacterial DNA -- we actually have not been able to get good sequence on that DNA as of the week before this presentation.
But what you can see here is that from these three storage mites and this one

house dust mite, we're getting, once again, predominantly or exclusively Bartonella species of various stripes.
I should add that a head-to-head comparison of these sequences to each other indicates that we are getting multiple organisms. This is not all one clone that we are sequencing over and over and over again with minor errors.
We are actually getting differences in key locations that suggest that this is not a homogeneous population of one species in these mites but rather multiple different species living in a community, as actually you see from other studies of symbiotic bacteria that live in insects of various sorts.

So our conclusion is that D. farinae endotoxin is high and is associated with the presence of Bartonella DNA. And we obviously did our original experiments in mites. We have shown this in mite extracts

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and actually this is an old slide because now we've shown it in four out of five of the wild mite species.

So our next step is to do a somewhat more detailed population analysis. And this is going to require some more microbiologic ecology work than we've done so far in terms of really trying to get a fine idea of what these populations are like.

We are going to go back now that we now that this is Bartonella with some certainty. We're going to go back and work with our microbiologists about actually culturing them out. And we're going to do a more detailed endotoxin analysis to see if we can verify that this is what is going on.

I should hasten to emphasize that we are still not sure what we're going to do with this. And we're still very much in the research phase of deciding what, if anything, needs to be done about this. But this is a set of persistent and interesting observations

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that we feel that we should be continuing on to the next steps.

You know memory plays funny tricks. I would be happy to take questions on that first part of the talk.

Dr. Atkins, is that okay with you?

CHAIR ATKINS: No, that would be great.

DR. SLATER: Yes. So why don't we stop here for a minute and if there are any questions about the -- yes?

DR. MARTIN: Jay, are you going to look at the fire ant extracts? It would seem like that would be an interesting piece to this.

DR. SLATER: You're absolutely correct. It would be a very interesting piece. We have not looked at that.

You know those are whole body extracts as opposed to venom extracts. The expectation would be that we might find something. And I think that would be of

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interest. And we failed to do so.
I think that would be a worthwhile avenue to pursue at this point because we have all the tools developed. So it would be straightforward.
Dr. Shepherd?
MEMBER SHEPHERD: Jay, there is the immediate reaction that this is a negative and perhaps represents a risk. Is there any data that this is actually a positive? That D. farinae immunotherapy -- isolated D. farinae immunotherapy is more efficacious because of the endotoxin? I mean you could certainly argue that would be the case.
DR. SLATER: Yes, you know, certainly from very early on after we made these initial observations, it was clear to us that there was at least a possibility that there was a beneficial effect in terms of the therapy -- the therapeutic options with these products.
And I think it is to the credit of
Page 102
the Division and the Office that we didn't immediately jump on this as a negative option. Right now we are treating it, I think, as a neutral observation. And I think we have good reason to do that. And we're pursuing it and trying to learn as much as we can.
But certainly when I first presented this work at the Academy of Allergy several years ago, other members of the Academy, you know, sort of introduced that idea that this might actually be contributing to the efficacy of allergen immunotherapy.
But right now we have no data whatever one way or another.
CHAIR ATKINS: But I thought you had another mite that didn't have Bartonella in it. One does and one doesn't, right?
DR. SLATER: I'm sorry?
CHAIR ATKINS: Well, the pteronyssinus didn't have it? One of them --

21 DR. SLATER: They both have -- so
22 the --
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1 CHAIR ATKINS: They both have
2 endotoxin but I thought Bartonella was in one
3 and not the other. Is that wrong?
4 DR. SLATER: The difference
5 between D. farinae and D. pteronyssinus
6 appears to be quantitative and not qualitative
7 at this point.
8 In other words, actually with the
9 exception of that one experiment that I showed
10 you, we actually are able to detect bacterial
11 DNA in both species although a greater number
12 of copies. And when we analyze the sequences
13 of that DNA, we actually find the same
14 distributive pattern.
15 So we're not -- I think it is a
16 quantitative difference and obviously --
17 ironically it is the quantitative difference
18 that first pushed us in the direction of
19 studying this at all in terms of the amount of
20 endotoxin.
21 But it turns out in the end that
22 both species contain Bartonella, at least as
Page 104
1 far as we can tell. But that one seems to
2 contain more than others.
3 MEMBER SHEPHERD: I realize you've
4 been looking in the lab. Is there any
5 consideration going to patients that are
6 receiving D. farinae and see if they have
7 antibodies to Bartonella over a control group?
8 DR. SLATER: We never thought of
9 doing that. That is a very interesting idea.
10 We've actually not identified
11 Bartonella-associated proteins although we
12 haven't looked. I think the first question
13 would be whether we can actually identify
14 bacterial proteins in the extracts.
15 So remember we've identified
16 endotoxin in the extracts. We've identified
17 DNA. But we haven't made that link.
18 But it would be -- it would
19 certainly drive us in the direction of looking
20 carefully at that if we found that individuals

who had received mite immunotherapy had Bartonella antibodies whereas those who
Page 105
hadn't, a matched group, did not or had lower titers. That would be very interesting. And possibly a more sensitive way of looking at it. So it is very interesting.
DR. NELSON: And I had the same thought but in also not looking at only the humoral response but the T cell mediated response and the possible generation of peptides. So perhaps non-intact protein but any stretches of amino acid in a cellular response.
DR. SLATER: Yes.
DR. NELSON: Similarly, have you done any analysis of the isolated genomic DNA from bacteria for content of immunostimulatory sequences that may serve as the adjuvant, perhaps the efficacy piece?
DR. SLATER: No, no, we haven't done that. But that's clearly worth looking at as well.
CHAIR ATKINS: Is there any data about evidence of antibodies to Bartonella in
Page 106
the general population? I mean because we're all exposed to dust mites on a regular basis. So --
DR. SLATER: I don't know. But before we do Dr. Shepherd's study, we'd have to assess that. That's right.
MEMBER COX: I don't know if I missed this. I don't think you covered this. But I know in Europe, they do treat single dust mites, D. farinae, pteronyssinus. I don't think there is an answer to this but has there been any differences in safety or efficacy seen in the two individual mite populations that might have been treated versus the U.S. where we almost exclusively use mixed mites, correct? Would you agree?
DR. SLATER: Well, first of all, I don't think we almost exclusively use mixed mites. I think there are many practitioners, myself included, who would treat with one mite

or the other, depending on the skin test pattern.

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But we've not solicited those data. I think it would be interesting data to have, especially if we had a good surveillance system for adverse events. Likewise, if we had a good system for assessing the efficacy of therapy.

And, again, my instinct is that it would be more productive to look at differences in efficacy based on the endotoxin content.

I really don't think, based on the existing surveillance system that we have, that we are getting any difference in signal from the two different species of mites nor are we getting any signal that mites, in particular, are more of a problem than, for instance, pollen extracts.

I think certainly Dr. Lockey's data suggests that, you know, pollen extracts may be the greater offenders in terms of adverse events than mites.

MEMBER COX: You know we've got an

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immunotherapy safety surveillance with both organizations that David Bernstein has just completed analysis and it was just presented as a late breaking.

And in this particular survey, we've actually asked for the different grades of systemic. So we're going to be analyzing a lot more data than we did in our previous surveys.

But I agree. I don't think we're going to see a pattern where it is, per se, dust mites are not as safe. And the pollen is probably related to height of pollen season, which is what we saw in the previous survey.

DR. SLATER: Well, thank you for bringing that up. I actually spoke to Dr. Bernstein precisely about this issue the day before yesterday. And he seemed to think that the next step of his project would be to go back and contact individuals who had reported

these adverse events and to try to get some
data from them.
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But the data aren't there now.
But is that true that you're planning on going
back to do that?
MEMBER COX: That's exactly -- it
is a co-funded project, for those who aren't
familiar, of the College and the Academy. And
it is sort of the fourth survey. Dick Lockey
started it dating back to 1945. And this is
the fourth survey.
It is an e-mail survey. We had
the highest response rate, which was about 476
respondents representing about 1,500
practitioners because it was one respondent
per practice.
And the good news is last year,
for the first time, we had no fatalities
reported. In the past, it has been about four
to five a year.
We also, for the first time, asked
them to give us the number of Grade 1, Grade
2, Grade 3 and we gave them a classification.
And there is a paid assistant who is going to
Page 110
do the follow up, contact them. And we can do
any types of analysis, looking at the Grade
3s, looking at what they might be associated
with what we call the long survey.
MEMBER HAMILTON: Could I ask --
I'm sorry.
MEMBER SHEPHERD: Can we ask Dr.
Plunkett if he knows and/or is able to tell us
a sense of sales in the U.S., how many
practitioners do used mixed mite extract D.
farinae and pteronyssinus versus one or the
other?
DR. PLUNKETT: Well, I really
don't know how that breaks out. It would be
just an impression from seeing my experience
at looking at panels and those kind of things.
But I really don't know.
I think it is significant. But I
think most people test for both mites. And
whether they get positives for both probably

happens probably 80 percent of the time.
So it would make sense to treat
Page 111
with a mix, I guess, in that sense.
CHAIR ATKINS: Dr. Hamilton, did
you have a comment?
MEMBER HAMILTON: I wanted to ask
in your work with Larry Arlian, has he
actually investigated using antibiotics in the
media to eliminate the presence of bacteria?
DR. SLATER: We've had discussions
about this. I don't really want to say
because I'm not exactly sure what the answers
were because these discussions were a couple
of years ago.
I'm not sure that he did this.
But I believe that attempts have been made to
grow the mites in the presence of
antimicrobials. And it had a dramatic effect
on the mites themselves. But I'm reluctant to
go into any greater detail about that.
MEMBER HAMILTON: So is the
thought that the Bartonella are in the
gastrointestinal tracts of the mite? And if
so, do we know that bacterial composition of
Page 112
the gut of a dust mite? And can we focus in
on other bacterial to look at?
DR. SLATER: Well, that's the
thought but only by analogy. There's a very
rich literature about bacteria living in the
guts and living in other internal organs of
various insects and arachnids. This is not an
uncommon event.
Some of these bacteria can have
profound effects, not necessarily beneficial
effects, on their host organisms, including
shifting gender ratios within the populations
based on whether they are parasitized or not.
So there is a lot of literature about that.
For the most part, these are
present in the gut. But they can be present
in other organs. They are transmitted
vertically in these cases.
And so -- but, again, everything
that we know about dust mites is by analogy

with those other studies. And I don't know directly.

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Shall I go on?

CHAIR ATKINS: Yes, please.

DR. SLATER: Okay. Okay, so the next study is an antibody-based multiplex bead assay to determine the potency and composition of allergen extracts.

And this is work that Nicky deVore, in our lab, is really taking -- well, she's doing almost all of the work -- and has for many years now. So this is really her project.

Her predecessor in the lab, Jonny Finlay, did some early work in terms of the antibody development.

Susan Huynh is a post-back fellow in the lab. And she's helping Nicky.

And Katya Dobrovolskaia is one of our biologists. And she's also contributing to the -- significantly to the work of this project.

So now we're going to go back to a topic that we touched on in Dr. Rabin's

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presentation. That is how do we measure allergen potency. But I'm taking a somewhat different angle than Dr. Rabin did. And I just want to sort of step back a little bit.

What Dr. Rabin was addressing was a proposal to look at improving our ability to measure specific allergens that we already measure and that we've already made a regulatory decision based on a great deal of clinical data and a great deal of clinical studies done by our predecessors, on whose shoulders we stand, that Amb a 1 was really the critical allergen in ragweed and that Fel d 1 and cat albumin were the two relevant allergens for cat allergy.

And so what Dr. Rabin was describing was a way of improving our ability to quantify Amb a 1 and Fel d 1. And possibly to start quantifying cat albumin in a way that we don't now using technological improvements

that have the advantage of performing better. But, in addition, have the

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advantage of being technologically accessible to just about everybody. These are really standard techniques that Dr. Rabin, I think, is hoping to be able to put into service for these particular extracts.

We're now going to talk about a very different situation and we're going to talk about the situation of the extracts in which we are measuring the overall potency.

I gave you this long preamble because I'm actually going to talk about cat and ragweed extracts also.

But we're only using those as an early model to study. We're not actually talking about applying this method to cat and ragweed extracts at all.

So how do we measure potency? We measure total protein for the hymenoptera. For cat and ragweed, we know what the specific allergens are and we have a specific allergen assay for each of these.

And for grasses and mites, we are

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not sure from a regulatory point of view what the relevant allergens are. And we choose many years ago to look at overall allergenicity using pooled human antisera.

The problem with that approach, which we really started to recognize first in 2000 in an unrelated study is that we're not sure that that overall allergenicity method will actually detect the specific loss of a single allergen.

I've already told you that for the mite and the grass pollen extracts, we don't know what allergen we care about. Otherwise we would just measure those. But the fact is as science advances we do actually learn what allergens we care about.

And we develop the ability to look at whether our overall allergenicity method can actually detect fluctuations in those specific allergen levels. And when we did

this in the course of this study, we actually were disappointed in the results.

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This was actually a study we did - - actually it was started before I came to the lab in 1998 -- on the stability of house dust, mite allergen extracts in glycerinated solutions.

And basically to make a very long story short, they took these different mite extracts that were glycerinated and they subjected them to a whole number of different abusive treatments as well as various different storage methods.

One of the abusive treatments was we actually froze them in the minus 80, which you could predict wouldn't do very good things for it. And not surprisingly, the Der p 1, Der p 2, Der f 1, Der f 2 levels dropped dramatically. But oddly enough, the overall potency by competition ELISA remained just about the same.

Well, there are lots of different interpretations of that. The best interpretation is that you are inducing

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conformational changes that your specific antibodies and your specific allergen measures are sensitive to. But that your polyclonal antiserum may not be sensitive to.

But that led to the sort of uncomfortable conclusion that you could conceivably eliminate an entire allergen from your mix and not be able to detect it with a change in your overall allergenicity assay.

So the dilemma that we really started to confront back in 2000 when we reported these data was that in order to measure specific allergens, you need to know which allergens you care about. Otherwise you can't design your assay.

But if you look at overall allergenicity, you may be unable to detect the absence of specific and potentially important allergens.

Now in subsequent studies, we

showed that this is not a deficit in the competition ELISA that we use. The

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competition ELISA is a terrific, strong, robust, precise, accurate assay. The problem is in the sera that you use to put your competition ELISA into effect. And we thought about possible solutions. And this is not only -- I don't really think it is a problem for grass and mite extracts but it is a problem for future allergen standardization techniques. And it seemed to us that there were really two possible solutions. And the solution was really to divide up the signals. You see with the competition ELISA, you are using a polyclonal antiserum pooled from many, many different allergic individuals and you are generating a single signal out of that. You are generating a relative potency. In fact, what you are doing, as you do with all polyclonal antiserums, is you are doing hundreds, maybe even thousands of different assays, none of which has really been optimized on its own, but only it has

Page 120

been optimized in the aggregate, and in which you are expressing a single integrated signal. What we were hoping to do was to attempt to divide the signal up. Well, if you divide the signal, you can always add it back up again and get an overall potency. But then you get individual signals that you can actually look at. We already know how to divide the signal by separating the allergens. That's called a Western blot. But what we wanted to try to do was to divide the signal by separating the antibodies. And the advantage to us of doing that is a little hard to get your hands around. We wanted to confront the situation, German cockroach, as an example, in which we really don't know what the important allergens are. And we actually did this study with NNID and we are quite convinced that we don't know

that a signal or even two allergens is critically important for German cockroach.

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We'd like to go ahead and standardize that using an overall measure of potency. But we'd like to build into our method the ability to detect individual signals even before they have a name.

And using the antibody approach, we can do that. We can actually immunize animals. We can actually get immune responses. And we can get signals to antigens that we haven't even identified yet, okay?

And that's the attraction of this.

What we're really aiming for, our long-term goal with this, is to be able to develop a method in which we can identify allergens that have yet to be identified.

So that we can go back into our database, pull out data as new science evolves, and say gee, okay, we know about that allergen. Not only do we know about that allergen but we know how much of that allergen we've had in each of our extracts since we implemented this assay five years ago.

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So our aim is to develop a multiplex antibody-based method for profiling complex allergen mixtures. And to implement that, we need to develop antibodies, we need to develop the assay.

We're going to apply this -- and the data I'm going to show you applies this to cat and ragweed, which was an effort to start out with simple extracts that we could get our hands around and really know what we're dealing with. In fact, as I'll explain to you later, we may have made our job more difficult by using cat and ragweed in a peculiar way.

And then ultimately we want to apply this to our current efforts to standardize German cockroach allergen.

So first we are going to talk about the antibodies. Now we developed recombinant clonal antibodies by injecting chickens with the allergen of interest. As

21 Dr. deVore explained when she presented these
22 data just a couple of days ago, the chicken
Page 123
1 has certain technological advantages in terms
2 of amplification. There is really only one
3 copy number of heavy and one copy number of
4 light chain. So you don't need to have
5 multiple primer sets in order to amplify them.
6 You can amplify them with single primer sets
7 for each.
8 And, in addition, there's at least
9 a theoretical advantage that you are going to
10 get a more robust response to mammalian
11 allergens in an avian source than you will in
12 other mammalian sources. So that that is
13 theoretical, we haven't demonstrated yet. But
14 it was a reasonable approach and it certainly
15 worked for us.
16 Once you detect a strong immune
17 response in the chicken, which, by the way,
18 you detect in the yolk of the eggs that the
19 chicken lays, you can sacrifice the chicken,
20 remove the bone marrow and spleen and purify
21 the total RNA, perform PCR to amplify the
22 antibody repertoire.
Page 124
1 You can digest the PCR products
2 and ligate them into a vector. And then that
3 vector contains the entire antibody library.
4 You can electroporate that into E. coli along
5 with a helper phage.
6 Then the scFv is expressed as part
7 of the PIII coat protein on the surface of the
8 phage, which allow you to select based on a
9 phage-display approach.
10 So we did this with Amb a 1 clones
11 and we looked at these Amb a 1 clones -- by
12 the way, in this experiment, we immunized the
13 chicken with cat and ragweed but we actually
14 pulled out the antibodies based on selective
15 phage display -- and I don't have to dwell on
16 this but basically we were able to pull out
17 selective Amb a 1 clones that recognized
18 specific allergens.
19 These are the Amb a 1 clones that
20 recognize only ragweed and the Amb a 1 and

21 they don't recognize the cat extracts.
22 Conversely, the anti-Fel d 1 clones recognized
Page 125
1 Fel d 1 and cat hair but don't recognize Amb
2 a 1 and ragweed.
3 In terms of developing the assay,
4 we actually spent a couple of years working on
5 the microarray approach. And then very wisely
6 gave it up for the microbead approach. And
7 the microbead approach just has been much
8 better in terms of assay feasibility and
9 performance.
10 The surfaces of each of these --
11 these are polystyrene microbeads. This is the
12 Luminex technology. They are coated with
13 carboxylic acid groups. Using EDC and sulfa-
14 NHS recombinant antibodies can easily be
15 covalently attached to the bead surface via an
16 amirite bond.
17 There we go. And each bead type
18 can be bound to specific recombinant
19 antibodies. So theoretically, these beads
20 have a color to them. And theoretically,
21 there are a hundred different colors that are
22 there.
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1 In fact, the ability of the
2 machine to discriminate against adjoining
3 beads is not as wonderful as you'd expect it
4 to be. But certainly you can discriminate
5 many of these beads from each.
6 And if you attach specific
7 antibodies to each of the beads, you can then
8 put, again optimistically, up to 100 different
9 bead types in a single well in a 96-well
10 plate.
11 Each well then contains the same
12 mixture of different beads. And in this case,
13 we did six different beads bound to six
14 different anti-Fel d 1 recombinant antibodies.
15 We did extract dilutions going across the
16 rows.
17 And then you have your antibody-
18 coated bead. You have the Fel d 1 in the
19 allergen extract. We have specific but
20 polyclonal rabbit sera that recognized Fel d

21 1 that we come back with. And then you come
22 with a biotinilated anti-rabbit antibody. And
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1 then streptavidin bound to RPE, which we can
2 then detect as our signal.
3 And, again, in the Luminex
4 machine, you can pull the beads up in a single
5 file into the detection chamber. There is a
6 laser that excites the dyes within the beads.
7 The dyes emit distinct photons that are picked
8 up by the Luminex concurrently with getting an
9 output signal of the median fluorescence index
10 from the RPE bound to the specific antibodies
11 on the surface.
12 And this is the kind of dose
13 response curve, obviously an ideal one, but
14 remarkably, in our actual experiments, we get
15 pretty good curves. And there is a maximum
16 and a minimum and a slope and an EC50.
17 And it is by comparing the EC50s
18 of a standard cat hair and a sample cat hair
19 extract that we can actually get the ratio of
20 these two EC50s and get a relative potency
21 using analytical methods that I think you are
22 all pretty much familiar with.
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1 So then in applying this to cat
2 and to ragweed, this is the summary of many,
3 many months of work, which, you know, I get to
4 get up and summarize in two slides. But other
5 people, obviously, did all the hard work.
6 Basically we found that the
7 average calculated potencies of ragweed
8 extract vary greatly when the anti-Amb a 1
9 scFvs are used alone or in groups. But the
10 potency of the ragweed extracts could be
11 accurately computed from the extracts with
12 known potencies using this microbead method.
13 And here what you have is a
14 comparison of for four allergen extracts of
15 the potency of these four extracts using the
16 RID method and using the microbead assay
17 method. And what you can see is that the
18 numbers that we get with the microbead method
19 certainly fall within the standard deviation
20 of the RID method.

What you can also see -- and this is one of the beauties of this method -- is

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that the data that we get are, for the most part, tighter than the data that we get with the RID. So it really quite a nice approach.

But -- and let me go ahead and show you the data with the anti-Fel d 1 data.

Again, one of our concerns was -- and this is a problem -- but one of our concerns is that when you mix beads, you actually get different results for when you analyze each bead individually.

And remember I told you that I was going to explain to you why I think starting out with cat and ragweed might have been a mistake even though it was conceptually simpler, I think we're getting substantial interference because we're recognizing essentially one protein in each of these extracts.

And even though the proteins we have different epitopes and actually Dr. deVore showed that there were different behaviors of these different epitopes, that by

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doing this, we were actually causing there to be some interference, which is a problem that we probably won't have when we're analyzing more complex mixtures.

But in any case, we were able to show the potencies of the cat extracts could be accurately computed from extracts with known potencies using the microbead method.

And here this is in Fel d 1 units.

You can see here that -- now, in this case, even though these numbers are fairly similar, they are not actually in each other's standard deviations. But in all the other cases, they are.

So we're pleased with this method.

And certainly we feel like we've worked out the major technological problems with it. And now we'd like to turn our sights on to a more complex problem. And that is the problem of German cockroach allergen standardization.

To do that, we actually contracted
out with a company called Millegen to use a
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library that we made but to screen it and to
develop ideally as many as 50 clones that
recognize German roach extract.
Initially what they did was they
selected 250 positive clones. They sequenced
these 250 clones and identified 150 unique
clones. You can see why we contracted this
out.
They selected 85 of these based on
their expression characteristics to express a
soluble form and to analyze by ELISA. And
then they shipped us the 50 best clones and
their plasmids to work with.
And for the last several months,
we've been working with these clones.
Needless to say, they don't all function quite
as well as we had hoped but we do have the
ability of going back in and getting more out.
But we are working with these and we are
hoping to do several things to try to make
this assay work.
Obviously we want to bind these
Page 132
soluble scFvs to bead-bound known allergens
and to see how they actually react. We want
to inhibition studies using known allergens.
We want to analyze the scFv binding patterns
by Western blot. We want to identify the scFv
recognized allergens by N-terminal sequencing.
Some of this work we're actually
doing in our lab right now. Actually Ms.
Dobrovolskaia is doing the 2D blots or is in
the process of doing the 2D blots to try to
identify these. We will be working with our
core facility to sequence the spots that are
recognized.
We are working as well with Dr.
Judith Woodfolk at University of Virginia who
has collaborated with us before in terms of
working on known cockroach antigens and the
antibody responses to them.
So we're hoping to work on this
antibody set to apply it to this technique.

21 And we're optimistic that this is something
22 that we are going to be able to use with the
Page 133
1 complex mixtures.
2 Let me just wrap up and then we
3 can have any questions about this. Now,
4 again, I get to brag about Ron's work. I'm
5 going to show you the publications. This is
6 only from the last four and a half or five
7 years.
8 Ron has not only a very active lab
9 publishing their own work but he's also an
10 active collaborator with other groups at NIH
11 and at the Vaccine Center. He and I both get
12 invited to write review articles on a regular
13 basis. And these are three that he has done
14 in the last couple of years.
15 We've also been fortunate that
16 we've published several articles from our
17 group, both in terms of primary work in the
18 lab and collaborative work with other groups
19 that you can see going back several years.
20 And a set of review articles as well.
21 We are fortunate to have really --
22 you know we are in a part of the FDA that
Page 134
1 enthusiastically supports the
2 researcher/reviewer model. We've gotten
3 really very, very generous intramural support
4 from the FDA.
5 Critical Path money is a separate
6 category but don't be fooled. That's
7 intramural money as well. This is a special
8 approach towards funding research that
9 identifies especially critical work towards
10 product development with an aim towards
11 cooperation between FDA labs and labs outside
12 the FDA.
13 But again if you're lumping and
14 saying is this FDA money, this is all FDA
15 money. And then Ron Rabin especially has been
16 very successful at competing for extramural
17 funds.
18 You are probably all aware that
19 being a federal agency we are limited in our
20 approach to extramural funding. But even with

those limitations, which obviously we observe scrupulously, Ron has been an extremely --

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really one of the most successful people in the Division in terms of securing external money.

We have site visits of our lab. And those site visits, of course, the visitors come out of this group and the results of those site visits are brought back to this Advisory Committee for review.

I was fortunate that when I came on as Lab Chief in 1998 they had just had a site visit. So I didn't need to have one until 2002. That site visit was aimed largely at reviewing my performance. The 2006 site visit was largely aimed at reviewing Dr. Rabin's performance. And we have another one coming up in the spring of 2010.

And that's the end of my presentation. I'm very happy to take questions or comments about any part of it.

CHAIR ATKINS: Yes, Dr. Hamilton?

MEMBER HAMILTON: Well, first, Jay, the Luminex system is a really powerful

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tool and I'm delighted that you have that tool in-house and that you are exploring its application. And maybe someday it will actually evolve into an actual application for monitoring therapeutic modalities and manufacturers.

I wanted to ask, since I saw a number of review articles on the recombinant allergenic materials, whether they will ever, in the future -- this is just a hypothetical question -- be considered as possible products for use in humans therapeutically? In the United States I mean since they are -- I think they've moved that direct in Europe already.

DR. SLATER: That's a good question. I mean we've certainly heard many, many presentations over many years about the promise of recombinant allergen products. There's really no conceptual impediment to this at all. As you know, FDA

has approved many recombinant proteins. I mean I believe in Dr. Rabin's

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article that you caught, there's actually a list of the recombinant proteins that have already been approved at FDA. They've been approved in multiple expression systems certainly consistent with the recombinant allergens that we know are out there and we know people are interested in studying. There are guidance documents in terms of the quality standards that need to be imposed. And there certainly, again, there's nothing conceptually missing in terms of these products being brought to us under IND and ultimately being brought to licensure. But we are -- in that sense, you understand, that our role is passive, that we receive these applications as they come in.

MEMBER HAMILTON: Thank you. I appreciate that.

CHAIR ATKINS: Yes, Dr. Grant?

MEMBER GRANT: The facts are that, as we mentioned to each other, there have not been any products in the United States brought

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to you in a while. And if you compare the science in other countries and the atmosphere, it has not been equal. And what can we do to bring to the American public the potential products that may very quickly be available to citizens of other countries? You are in a passive role absolutely. But we're here to advise you in ways of, you know, changing the climate or helping the manufacturers in the United States to make these available. The market is not a big one. And that's one of the things that I've been told by members of the pharmaceutical industry in the United States. They just don't have the funds to do the studies that would permit you to approve them.

DR. SLATER: We have -- the FDA is a law enforcement agency. It's job is to enforce the Food, Drug, and Cosmetic Act and

its amendments and the Public Health Service Act.

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The requirements for evaluating the safety and efficacy of these products will not change and rightly so. We have many mechanisms in place to assist investigators and sponsors as they wish to prepare their products for submission.

That being said, we have requirements. The requirements are there for the benefit of the consumers as well as the benefit for the study subjects and the INDs.

But I can tell you that we've had positive interactions with many investigators over this period. And, again, I don't think, to be honest, there is anything that we can do to encourage the situation more than we are already.

If anybody else from the Agency wishes to comment, they are welcome to.

DR. BLAKE: I'll make that comment.

First of all, I will not apologize to this group for hiring and promoting Dr.

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Slater up into my office. He is a wonderful, very great assistant in that office.

And it also kind of says my view of the importance of these products and what they should do. And there could be no other one that could exemplify knowledge between these two individuals here.

So yes, we do understand the importance of these products, the future of these products. We are currently trying to recruit another clinical person into that group to expand this group and to enlarge in it. We are trying to, in every way, encourage this group in doing that.

But as Jay indicated, we are a law enforcement agency with specific laws. And I've been with the Agency for some time -- this is my third life -- but I learned very quickly coming in there was three terms that I needed to remember in all cases.

21 Something has got to be safe,
22 potent, and effective. And those are the
Page 141
1 three words that we have to memorize.
2 And so going forward, we will
3 encourage and I think the Agency overall has
4 encouraged new products, trying to get away
5 from the support given to Jay as to try to get
6 through some of the things that need to be
7 done so that these products can come aboard.
8 But there's still -- we still have
9 to remember those three terms: safe, potent,
10 and effective.
11 CHAIR ATKINS: Dr. Shepherd?
12 MEMBER SHEPHERD: Jay, thanks so
13 much for going over that. Obviously terrific
14 work.
15 All your efforts at the present
16 time have been to analyze the materials for
17 immunotherapy for safe, potency, and
18 effectiveness. I presume you are on the verge
19 of getting applications for all the sublingual
20 materials.
21 Do you anticipate any changes in -
22 - if the current system for evaluation would
Page 142
1 be the same for the sublingual preparations?
2 DR. SLATER: Well, that's a good
3 question. So -- and actually I think Dr.
4 Rabin addressed some of these questions in one
5 of those review articles that he wrote.
6 The current method that we have
7 for evaluating the potency of our standardized
8 extracts, for most of them it ultimately goes
9 back to a series of quantitative intradermal
10 studies that were done with these extracts.
11 This includes the mite extracts, grass
12 extracts, the short ragweed, and even the
13 hymenoptera extracts.
14 Those evaluations are based on
15 certain assumptions about the extracts and the
16 immune response to them. That is that the
17 potency has to do with the IgE binding, that
18 the adverse events have to do with the IgE
19 binding, and that there is nothing in the
20 preparation that interferes with your ability

21 to do those kinds of assays.
22 With the newer products, that is
Page 143
1 not always the case. An engineered product
2 that no longer has an IgE binding site can't
3 be evaluated in that manner. A product that
4 has other interfering substances in it may not
5 be evaluable in that manner.
6 So we're learning now. And I'm
7 not commenting on sublingual versus other
8 routes of therapy. What we're learning now is
9 that with the new product forms and formats
10 that are out there, that we need to work with
11 the sponsors to develop potency assays.
12 The need to develop a potency
13 assay can't be avoided. We have to have a
14 potency assay for these extracts because it is
15 our best way of assuring that they are safe
16 and effective. And as I've said many times,
17 you actually can't do science with anything
18 unless you know what you are using.
19 So you need to have potency
20 assays. And we work with the manufacturers to
21 help them develop potency assays, hopefully
22 fairly early in their product development.
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1 This is not something that you want to have as
2 a last minute afterthought. This has got to
3 be something fairly early in the product
4 development.
5 But if you are asking are we
6 scientifically flexible and able to work with
7 the manufacturers for that, I can tell you
8 unequivocally yes. We are.
9 And we do recognize that there are
10 unique situations with unique product forms
11 and formats. And we work with the sponsors to
12 solve them.
13 Did that answer your question?
14 MEMBER COX: Dan?
15 CHAIR ATKINS: Sorry, Dr. Cox?
16 MEMBER COX: I have a question
17 regarding an earlier agenda. There were two
18 items that were on the agenda. One was the
19 Category 3A at allergen extracts, has that
20 been --

21 DR. SLATER: You're not allowed to
22 ask about things that we took off the agenda.
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1 MEMBER COX: Oh, okay, I'm sorry.
2 DR. SLATER: No, I'm just kidding.
3 I'm sorry. I'm sorry.
4 MEMBER COX: I don't remember that
5 in the orientation. Forgive me.
6 DR. SLATER: I'm sorry. You're
7 asking about Category 3A?
8 MEMBER COX: Correct.
9 DR. SLATER: Okay, well I can
10 answer something about it. I can't give you
11 a progress report but I can illuminate the
12 other people --
13 MEMBER COX: Okay.
14 DR. SLATER: -- on the Committee
15 as to what you're asking if you want. Would
16 you like me to do that?
17 MEMBER COX: Yes.
18 DR. SLATER: Okay. So when FDA
19 inherited -- allergenic products, like most
20 biologics, were actually regulated by the
21 Bureau of Biologics in NIH. I don't know if
22 anyone -- yes, did I say that correctly --
Page 146
1 thank you -- Bureau of Biologics in NIH until
2 1972.
3 In 1972, Congress recognized that
4 there might be a better way to do this and
5 transferred biologics over to FDA. FDA then
6 inherited a whole world of products that they
7 had never regulated before and put into place
8 a series of panels to review the efficacy and
9 safety of these products.
10 These panels were not unique to
11 allergenics. There were panels for all the
12 biological products.
13 The allergenics panel started to
14 meet in 1974. And I don't have a slide with
15 the roster. I've shown that in other talks.
16 But it was really the luminaries of the
17 allergy world at the time.
18 And these people worked very hard
19 for many years reviewing all of the then 1,500
20 allergenic products that were out there. And

21 they made some recommendations based on what
22 the FDA asked them to do.
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1 The FDA asked them to classify
2 products as either Category 1, which is safe,
3 effective, and not misbranded, that's good,
4 Category 2, which is either unsafe or
5 ineffective or misbranded, okay, Category 2
6 products can't be part of the world of
7 approved products.
8 Or the FDA originally permitted
9 these people to classify things as Category 3,
10 which basically was we don't have enough data
11 to decide for sure whether something is going
12 to be Category 1 or Category 2.
13 Subsequently -- actually while
14 this committee was still working -- FDA
15 changed its request and asked all Category 3A
16 products to be reclassified into either
17 Category 1 and 2. And this same committee
18 then came back and did their work again in the
19 early 1980s to reclassify these products as
20 either Category 1 or Category 2.
21 They made recommendations that for
22 a variety of reasons didn't get implemented.
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1 And then in about the year 2002, we began to
2 review what they had done and actually brought
3 into play all the literature that had
4 accumulated since the 1970s.
5 So we actually internally in our
6 group, in the Office of Vaccines, there were
7 about a dozen of us that basically spent a
8 couple of years reviewing all of the Category
9 3A products and making recommendations -- with
10 an eye towards making recommendations about
11 reclassifying them as Category 1 to Category
12 2.
13 So that was a long-winded
14 explanation of Dr. Cox's question. And in two
15 previous Advisory Committee meetings, we
16 actually gave extensive reports on how we were
17 going to approach this. And we even gave a
18 progress report as to how much progress we had
19 made.
20 What I can tell you is that we are

nearing the end of that process but, Dr. Cox, we were not actually ready to make a report to you at this time.

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That being said, the process, as we explained before, is really the completion of a process that was started 20 plus -- sorry, 37 years ago. So we are hoping at the end of 37 years or perhaps 38 years to complete this process. And you will certainly be hearing about this either at the next Advisory Committee meeting or perhaps before.

CHAIR ATKINS: Any other questions for Dr. Slater?

(No response.)

CHAIR ATKINS: Thank you very much. That's excellent.

It's now 10:57 and we're at the slot in the agenda for the open public hearing. Is there anyone in the audience who has a question for the Committee?

(No response.)

CHAIR ATKINS: No questions? Any other questions from the Committee?

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(No response.)

CHAIR ATKINS: Adjourned.

MS. DAPOLITO: Thank you, Dr. Atkins.

CHAIR ATKINS: Thank you.

(Whereupon, the above-entitled meeting was concluded at 10:59 a.m.)

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